METHODS OF ENHANCING CHEMOTHERAPY

FIELD OF THE INVENTION

The present invention relates generally to compositions and methods useful for treating cell proliferative disorders and more particularly to a method of enhancing the responsiveness of tumors to chemotherapy, increasing the dose of a chemotherapeutic agent that can be safely administered, and preventing the emergence of multidrug resistance (MDR). The present invention also provides a method for significantly enhancing oral bioavailability of chemotherapeutics.

BACKGROUND

There are three major types of treatment currently in use to treat neoplasms: surgery, radiation therapy, and chemotherapy. Cytotoxic chemotherapeutic agents include a variety of natural products, for example taxanes, such as paclitaxel and docetaxel; vinca alkaloids such as vinblastine, vincristine and vinorelbine; anthracyclines such as doxorubicin, daunorubicin and idarubicin; and epipodophyllotoxins such as etoposide and teniposide. The ability of these agents to cure neoplastic disease is extremely limited due to lack of tumor cell specificity, the presence of multi-drug resistant (MDR) tumor cells at the time of first diagnosis and the *de novo* emergence of multi-drug resistant tumor cells during treatment.

Cytotoxic chemotherapeutic agents frequently suppress lymphocyte and hematopoietic and stem cell production, destroy the normal cells lining the digestive tract, and are toxic to the cardiovascular and nervous systems. These dose-limiting toxicities usually prevent the use of cytotoxic agents at doses which could kill sufficient numbers of tumor cells to effect a cure. The use of taxanes, vinca alkaloids, and anthracyclines is also largely limited to parenteral routes of administration, due to lack of oral bioavailability. This is due, in part, to the normal expression of a protein called P-glycoprotein (P-gp) in intestinal epithelial cells. P-gp is an ATP-dependent membrane transport protein that pumps certain absorbed xenobiotics, such as chemotherapeutic agents, back into the lumen of the digestive tract.